

APOPTOSIS MEDIATED NEUROTOXICITY INDUCED BY β -AMYLOID AND PRP FRAGMENTS.

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Amyloid- β protein ($A\beta$) deposits in brain parenchyma and vessel walls is a major pathological feature of Alzheimer's disease (AD). Also in prion-related encephalopathies, altered form of prion protein (PrP) forms amyloid fibrils and accumulates in the brain of affected individuals. In both conditions the amyloid deposition is accompanied by nerve cell death, whose pathogenesis and the molecular basis are not understood. A dramatic cell loss was observed in rat primary hippocampal neurons chronically exposed (5-7 days) to micromolar concentrations of synthetic peptides homologous to $A\beta$ (β 25-35) or PrP(PrP106-126) fragments. Optical and electron microscopy examination of nerve cell nuclei exposed to both peptides presented a typical apoptotic morphology, with condensation of chromatin and fragmentation of the nucleus. According to morphological observations, agarose gel electrophoresis of DNA extracted from cultured cells after seven days of treatment with β 25-35 or PrP 106-126 revealed the characteristic pattern of fragmentation in multiples of ~200 base pairs. Intracellular neurotoxic mechanism was investigated by Northern blot and PCR analysis of expression of early genes (c-fos, c-jun, c-myc) and other proteins (p53, SGP-2, bcl-2, HSP70) potentially involved in apoptosis. With the exception of bcl-2 mRNA decrease, no consistent alterations of these mRNA expressions were found in neuronal cells exposed to β 25-35 or PrP 106-126. We also investigated the effects of 14-day exposure of rat astroglial cultures to micromolar concentrations of β 25-35 or PrP 106-126. PrP106-126 induced astroglial proliferation and hypertrophy while β 25-35 was unaffected. Both β 25-35 and PrP 106-126 have a β -sheet structure and exhibit self-aggregation properties demonstrated by light scattering and electron microscopy examination. Since the neurotoxicity of these peptides has been associated with their fibrillogenic activity, we synthesized amidated homologous β (25-35)NH₂ and PrP(106-126)NH₂ with low level amyloidogenic activity to directly test the relationship between amyloid fibrils and cell death.